Oncology Grand Rounds

New Agents and Strategies in PARP Inhibition in the Management of Common Cancers

Thursday, June 25, 2020

5:00 PM – 6:30 PM ET

Faculty

Emmanuel S Antonarakis, MD
Gretchen Santos Fulgencio, MSN, FNP-BC
Kathleen Moore, MD
Joyce O'Shaughnessy, MD
Michael J Pishvaian, MD, PhD
Deborah Wright, MSN, APRN, CNS

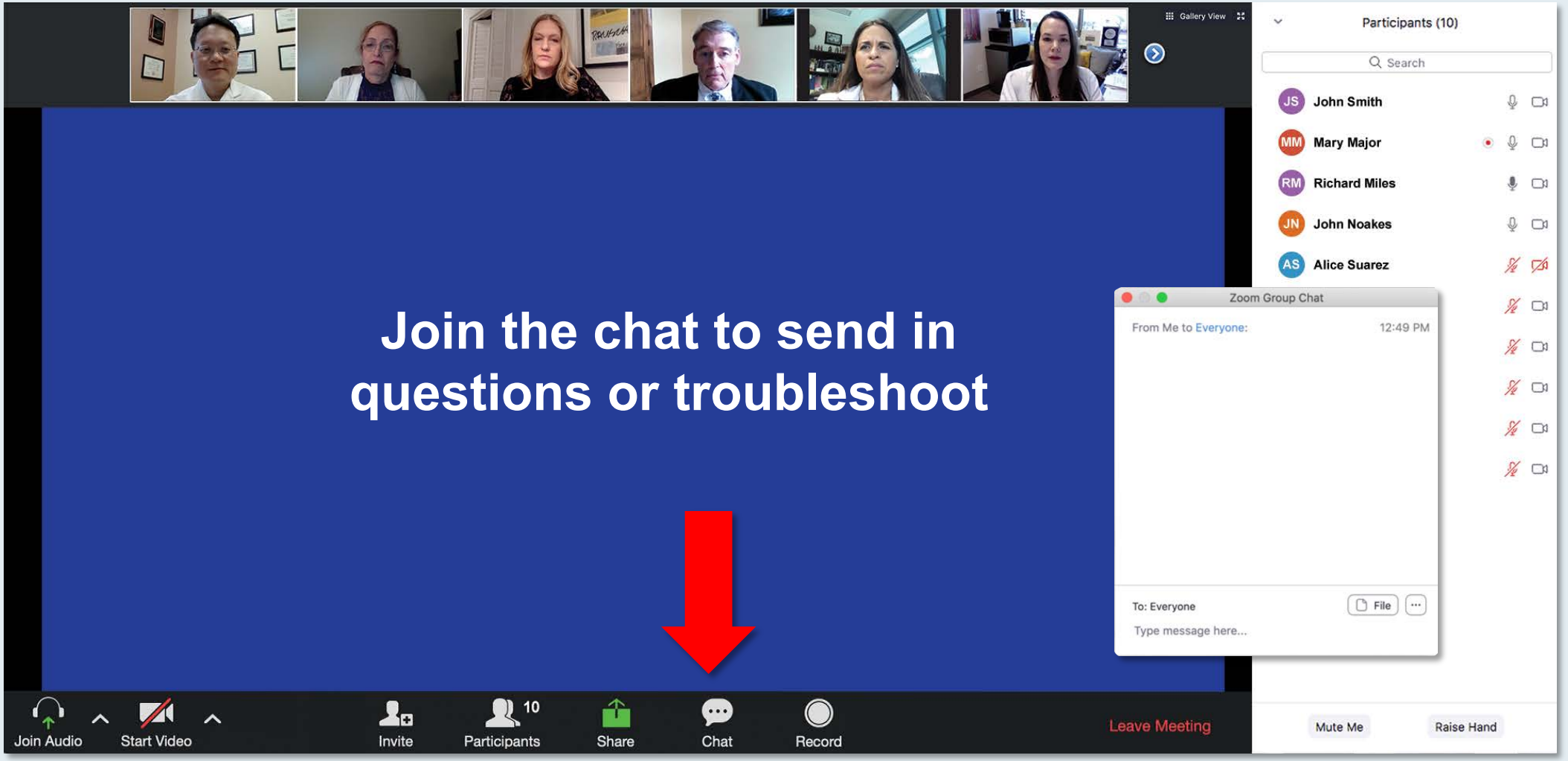
Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Familiarizing yourself with the Zoom interface

How to participate in the chat



About the Enduring Program

- This webinar is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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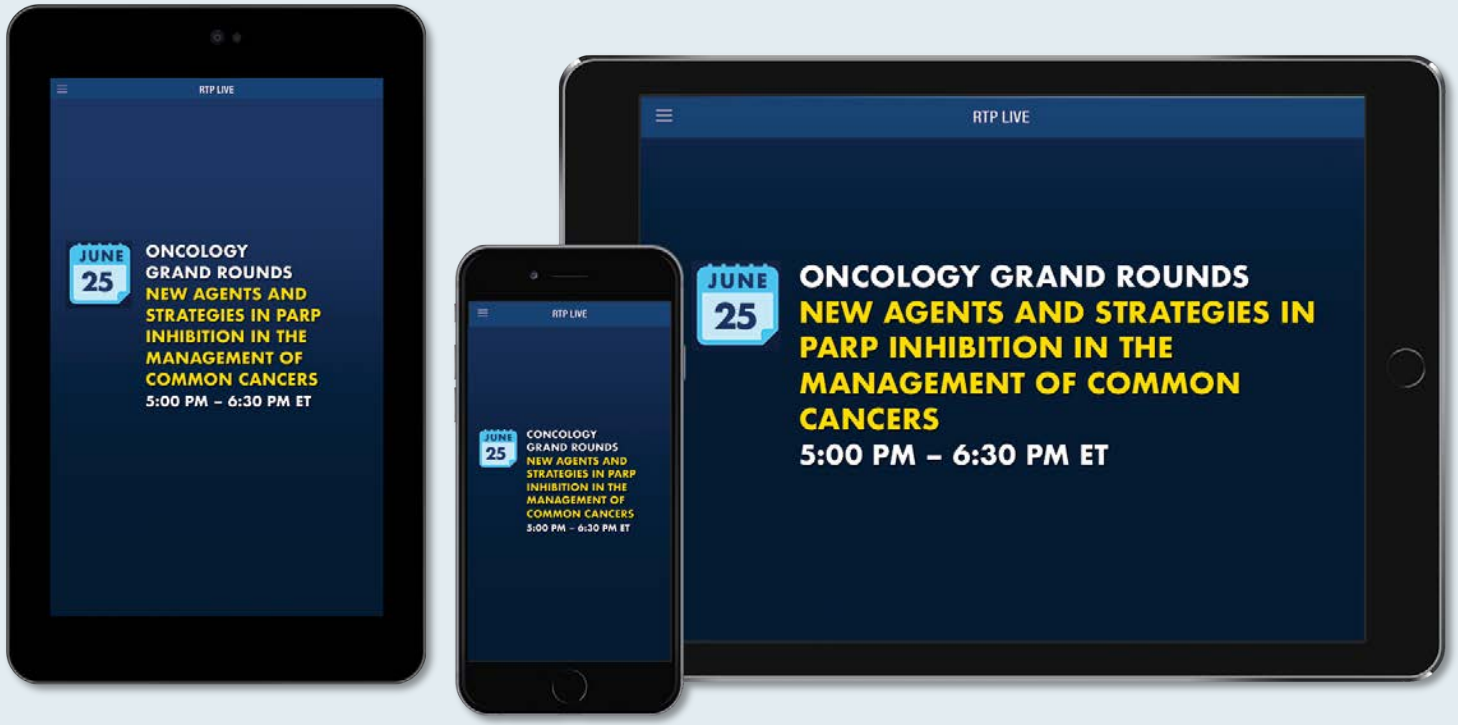

ONCOLOGY TODAY

WITH DR NEIL LOVE

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Clinical Investigator Perspectives on the Current and Future Management of Multiple Myeloma

A Meet The Professor Series

Friday, June 26, 2020
12:00 PM – 1:00 PM ET

Nikhil C Munshi, MD
Professor of Medicine, Harvard Medical School
Director of Basic and Correlative Science
Associate Director, Jerome Lipper Multiple Myeloma Center
Department of Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Co-provided by USF Health RTP RESEARCH TO PRACTICE

Oncology Grand Rounds

New Agents and Strategies in Prostate Cancer

Tuesday, June 30, 2020

5:00 PM – 6:30 PM ET

Faculty

Robert Dreicer, MD, MS
Kara M Olivier, NP, APRN-BC
Victoria Sinibaldi, RN, MS, CS, CANP, BC
Matthew R Smith, MD, PhD

Moderator

Neil Love, MD

Jointly provided by USF Health

RTP RESEARCH TO PRACTICE

Conversations with the Investigators: Prostate Cancer

Wednesday, July 1, 2020
5:00 PM – 6:00 PM ET

Faculty

Robert Dreicer, MD, MS
Daniel P Petrylak, MD
Christopher Sweeney, MBBS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

COVID-19 AND LUNG CANCER

What We Know, What We Don't Know and What It All Means for Current Patient Care – *A Live CME Webinar*

Thursday, July 2, 2020
12:00 PM – 1:00 PM ET

Moderator
Neil Love, MD

Faculty
Leora Horn, MD, MSc
Naiyer A Rizvi, MD
Lecia V Sequist, MD, MPH

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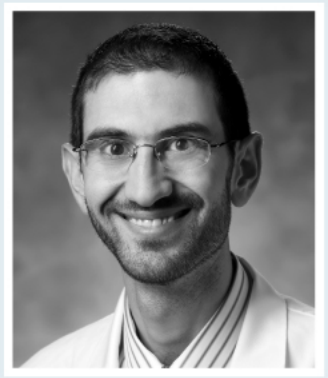
Research To Practice®



Emmanuel S Antonarakis, MD
The Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

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University of California, San Francisco
Berkeley, California

Kathleen Moore, MD
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

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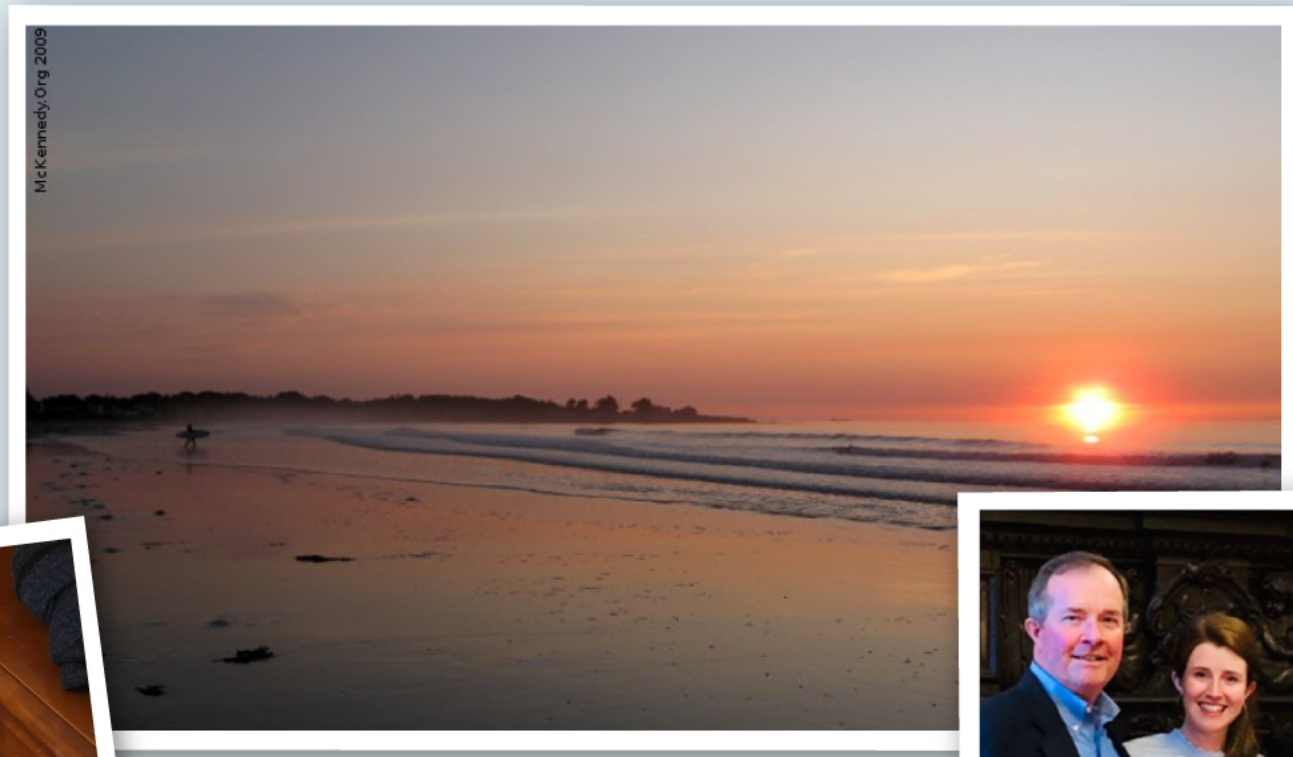
Dallas, Texas



Michael J Pishvaian, MD, PhD
NCR Kimmel Cancer Center at Sibley Memorial Hospital
Washington, DC

Deborah Wright, MSN, APRN, CNS
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

Agenda

Module 1: Overview of PARP Inhibitors — Biologic Rationale and Mechanism of Action

- Case Presentation: 47-year-old woman with ovarian cancer

Module 2: Side Effects and Toxicities of PARP Inhibitors

Module 3: PARP Inhibitors for Ovarian Cancer

Module 4: PARP Inhibitors for Breast Cancer

- Case Presentation: 34-year-old woman with ER-positive, HER2-negative breast cancer

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- Case Presentation: 67-year-old man with metastatic pancreatic cancer
- Case Presentation: 68-year-old man with metastatic pancreatic cancer

Module 6: PARP Inhibitors for Prostate Cancer

- Case Presentation: A man in his early 50s with metastatic prostate cancer
- Case Presentation: A 71-year-old man with metastatic prostate cancer

Module 1: Overview of PARP Inhibitors — Biologic Rationale and Mechanism of Action

Genomic assays, PARP sensitivity and biologic rationale for PARP inhibitors

- Germline versus somatic testing
- Role of liquid biopsy
- Mechanism of action, potency of PARP inhibitors; PARP trapping
- Approved PARP inhibitors

Each type of DNA damage is repaired by a specific process

	Base alkylation	DNA single strand breaks	Bulky adducts	Base mismatches, insertions and deletions	DNA double strand breaks
Repair pathway	Direct reversal	Base excision repair (BER)	Nucleotide excision repair (NER)	Mismatch repair	DSB repair → Non-homologous end joining (NHEJ); Homologous recombination repair (HRR)
		Involves PARP			**Involves BRCA1/2**

Courtesy of Kathleen N Moore, MD

1. Lord CJ and Ashworth A. *Nature.* 2012;481:287–293; 2. O'Connor MJ. *Mol Cell.* 2015;60:547–60

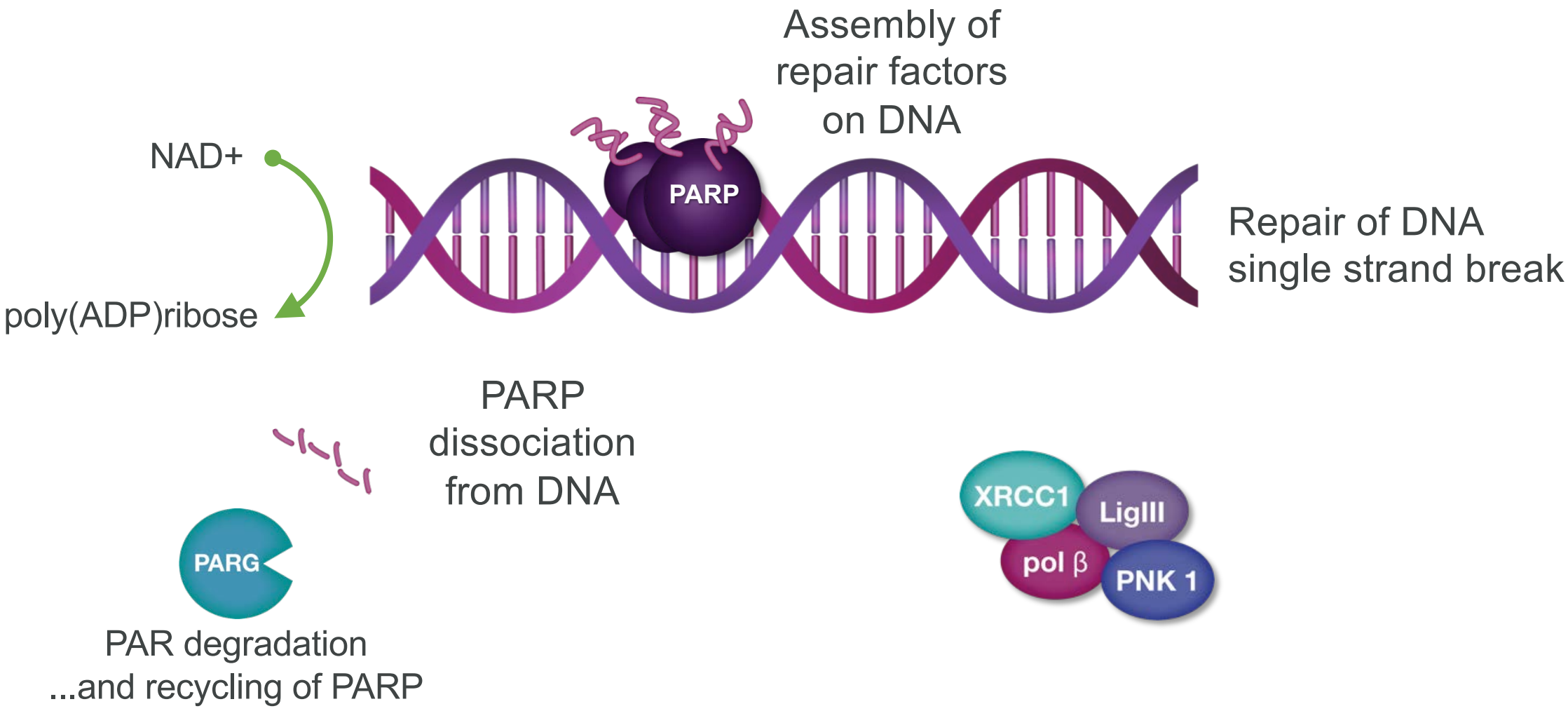
PARP facilitates single strand break repair

PARP recruitment

Courtesy of Kathleen N Moore, MD

- 1. Lord CJ and Ashworth A. *Nature.* 2012;481:287–293; 2. De Lorenzo SB et al. *Front Oncol*. 2013;3:228; 3. Curtin NJ. *Nature Rev Cancer.* 2012;12:801–817

PARP facilitates single strand break repair

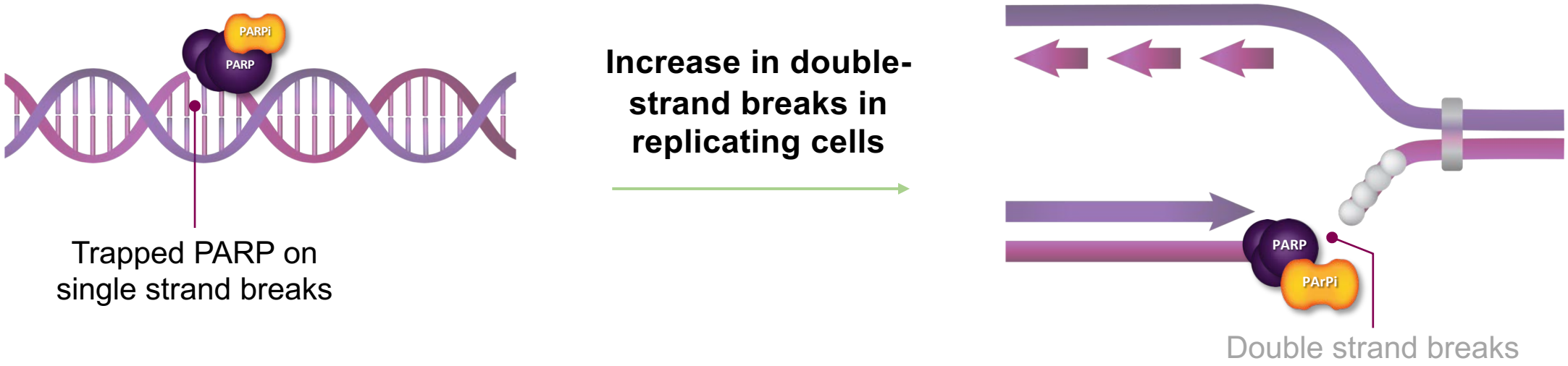


LigIII=LIG3alpha; NAD+=donor nicotinamide adenine dinucleotide; PAR=poly (ADP-ribose); PARG= poly (ADP-ribose) glycohydrolase; PARP=poly (ADP-ribose) polymerase; PNK=PaNtothenate Kinase 1; pol β=DNA polymerase β; XRCC1=X-ray repair cross-complementing protein 1

1. Lord CJ and Ashworth A. *Nature.* 2012;481:287–293; 2. De Lorenzo SB et al. *Front Oncol*. 2013;3:228; 3. Curtin NJ. *Nature Rev Cancer.* 2012;12:801–817; Javle N and Curtin NJ., *Br J Cancer*. 2011 Oct 11;105(8):1114-22

Courtesy of Kathleen N Moore, MD

Vulnerabilities in the ability of a cancer cell to repair dsDNB when paired with a PARP inhibitor can lead to faulty repair and cell death

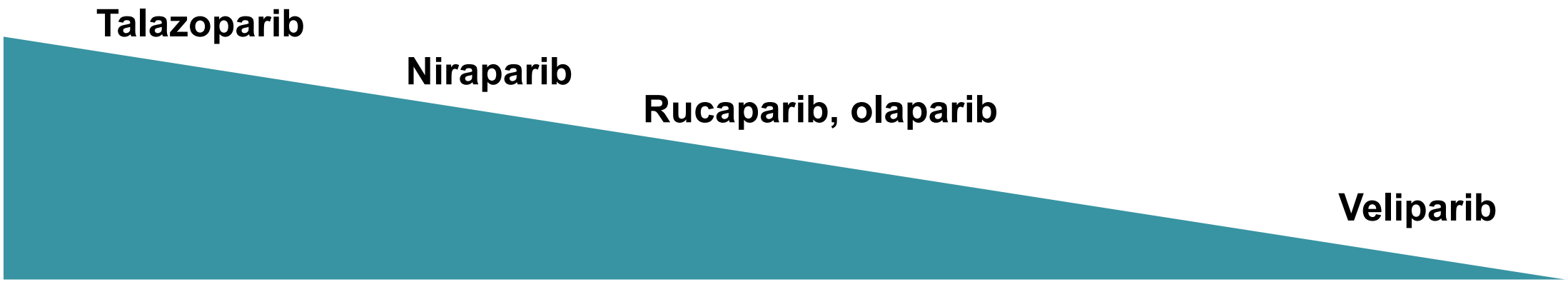


HRD=homologous recombination deficient; HRR=homologous recombination repair; PARP=poly (ADP-ribose) polymerase; SSB=single strand break

O'Connor MJ. *Mol Cell.* 2015;60:547–60

Courtesy of Kathleen N Moore, MD

PARP Targeting Potency: High to Low



Adapted from: Lord CJ, et al. *Science.* 2017;355:1152-1158.

Courtesy of Philip A Philip, MD, PhD, FRCP

FDA Approved and Late-Stage Investigational PARP Inhibitors

	Olaparib	Niraparib	Rucaparib	Talazoparib	Veliparib
Ovarian	• Front line • Plat-sensitive recurrent • Multiply relapsed	• Front line • Plat-sensitive recurrent • Multiply relapsed	• Plat-sensitive recurrent • Multiply relapsed	—	VELIA Ph3
Breast	• Metastatic	BRAVO Ph3	—	• Metastatic	—
Pancreatic	• Metastatic	—	—	—	—
Prostate	• Metastatic CRPC	Breakthrough therapy (GALAHAD) MAGNITUDE Ph3	• Metastatic CRPC	TALAPRO-2 Ph3	—

Olaparib PI, rev 5/2020; Niraparib PI, rev 4/2020; Rucaparib PI, rev 5/2020; Talazoparib PI, rev 3/2020; Clinicaltrials.gov, Accessed 6/2020

47-year-old woman with ovarian cancer (from the practice of Ms Wright)

- During routine robotic cholecystectomy, carcinomatosis noted
  - Pathology: Adenocarcinoma PAX8-positive, ER/PR-positive
  - Imaging: Large amount of ascites, peritoneal carcinomatosis with bilateral adnexal masses.
- Neo-adjuvant carboplatin/paclitaxel and oral BMI1 inhibitor x 3 cycles → interval cytoreductive surgery to no gross residual disease (Stage IIIC HGSOC), BRCA2 mutation
- Imaging after 3 more cycles of platinum doublet/study drug: CR, CA 125 normalized
- Olaparib maintenance 300 mg po bid
  - After 2 weeks: Stomatitis (Magic Mouthwash) → resolved
  - After 6 weeks: Hgb: 7.1, increased GERD after dosing (pantoprazole)
    - Dose reduction of olaparib due to transfusion x 2, Hgb now 10.0
- 4/30/2020: Dose reduced olaparib to 150mg po bid due to increased GERD
- Currently, patient has completed 5 cycles of maintenance therapy (CA 125: 6.7)
  - Considering prophylactic bilateral mastectomy with reconstruction

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Module 2: Side Effects and Toxicities of PARP Inhibitors

- Cytopenia
- Gastrointestinal toxicity
- Creatinine elevation
- ALT/AST elevation
- Risk of MDS/AML

Gastrointestinal side effects and cytopenias are class effects of PARP inhibitors, but the frequencies vary among available agents.

a. Agree
b. Disagree
c. I don’t know

Adverse Events: Class Effects and Specific Drug Differences

	Notes	Olaparib	Niraparib	Rucaparib	Talazoparib	Veliparib
Fatigue	50%-70%, mainly Gr1-2	✓	✓	✓	✓	✓
Hematologic AEs						
Anemia	40%-60%	✓	✓	✓	✓	✓ --
Thrombocytopenia	Niraparib dose adjustment, based on platelet counts	✓	✓ ++	✓	✓	✓
Neutropenia	~20%	✓	✓	✓	✓	✓
Gastrointestinal AEs						
Nausea/vomiting	Moderately emetic >30%	✓	✓	✓	✓	✓
Diarrhea	~33%	✓	✓	✓	✓	✓
Laboratory abnormalities						
ALT/AST elevation	5%-10% olaparib, niraparib; 34% rucaparib	✓ --	✓ --	✓ ++	✓ ++	?
Creatinine elevation	10%-12%	✓	✓	✓	**NR**	**NR**

Olaparib PI, rev 5/2020; Niraparib PI, rev 4/2020; Rucaparib PI, rev 5/2020; Talazoparib PI, rev 3/2020; Madariaga A et al. *Int J Gyn Cancer* 2020 April 9;[Online ahead of print]; Litton JK et al. *NEJM* 2018;379:753-63.

NR, not reported

Adverse Events: Class Effects and Specific Drug Differences

	Notes	Olaparib	Niraparib	Rucaparib	Talazoparib	Veliparib
Respiratory disorders						
Dyspnea +/- cough	10%-20%, usually Gr 1-2	✓	✓	✓	✓	NR
Nasopharyngitis	~10%	✓	✓	✓	✓	NR
Nervous system and psychiatric disorders						
Insomnia/headache	10%-25%, usually Gr 1-2	✓	✓	✓	✓	✓
Dermatologic toxicity						
Rash, photosensitivity		<1%	✓	✓++	NR	NR
Cardiovascular toxicity						
Hypertension, tachycardia, palpitation		1%	✓++	NR	NR	NR
Rare AEs						
MDS/AML	~1% of pts	✓	✓	✓	✓	✓

Olaparib PI, rev 5/2020; Niraparib PI, rev 4/2020; Rucaparib PI, rev 5/2020; Talazoparib PI, rev 3/2020; Madariaga A et al. *Int J Gyn Cancer* 2020 April 9;[Online ahead of print]; Litton JK et al. *NEJM* 2018;379:753-63.

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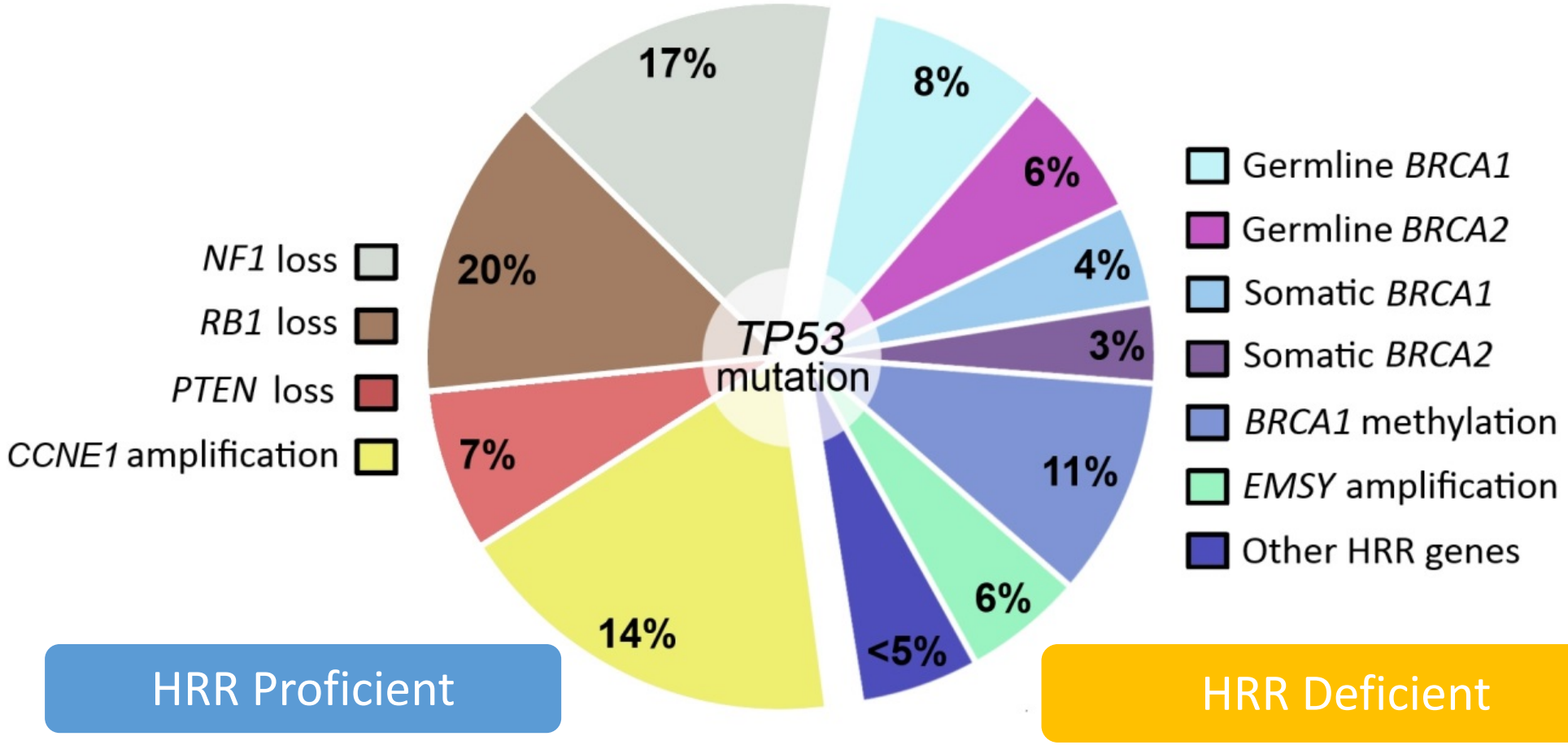
Module 3: PARP Inhibitors for Ovarian Cancer

- Genomic profile
- Prior trials in relapse setting: maintenance and monotherapy
- Key recent up-front data sets: SOLO-1, PRIMA, PAOLA-1, VELIA
- Current practice patterns
- Ongoing trials

A PARP inhibitor should be offered to or discussed as an option for patients with Stage III or Stage IV ovarian cancer, regardless of genomic profile.

a. Agree
b. Disagree
c. I don’t know

Rationale for PARP inhibitors in ovarian cancer: high grade serous ovarian cancer biology



- Hollis RL, et al. Cancer Biol Med. 2016; 13:236-247

Courtesy of Kathleen N Moore, MD

PARP inhibitor indications

	OLAPARIB[1-3]	TALAZOPARIB[4-6]	RUCAPARIB[7]	NIRAPARIB[8]
MoA	PARP-1, PARP-2, PARP-3 inhibitor	Dual-mechanism PARP inhibitor	PARP-1, PARP-2, PARP-3 inhibitor	PARP-1, PARP-2 inhibitor
Treatment Indication	Second-line or greater chemotherapy with deleterious or suspected g*BRCA*m HER2– mBC Third-line or greater chemotherapy with deleterious or suspected g*BRCA*m OC	Deleterious or suspected deleterious g*BRCA*m, HER2– locally advanced or mBC	Second-line or greater chemotherapy with deleterious g/s*BRCA*m OC	4th line or greater, HRD+, Plat sensitive
Maintenance Indication	Second-line maintenance for recurrent EOC, FTC, PPC First-line maintenance for high-risk advanced (FIGO stage III-IV) *BRCA*m high-grade EOC, FTC, PPC or with bevacizumab for HRD+	Not indicated	Second-line maintenance for recurrent EOC, FTC, PPC	Second-line maintenance for recurrent EOC, FTC, PPC First Line Maintenance following PR or CR – all comers
Recommended Dose	300 mg PO BID	1 mg PO QD	600 mg PO BID	300 mg PO QD
Approval Date(s)	January 2018; December 2014; August 2017; December 2018, May 2019	October 2018	December 2016 and April 2018	March 2017

BID, twice daily; FIGO, International Federation of Gynecology and Obstetric; FTC, fallopian tube cancer; g/s*BRCA*m, germline and/or somatic *BRCA* mutant; HER2–, human epidermal growth factor receptor 2 negative; HGSOC, high-grade serous ovarian cancer; MoA, mechanism of action; PPC, primary peritoneal cancer; PO, by mouth; QD, once daily.

1. Robson M, et al. Presented at: AACR 2018; April 14-18, 2018; Chicago, IL. 2. LYNPARZA [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017. 3. www.clinicaltrials.gov/NCT01844986. 4. www.clinicaltrials.gov/NCT01945775. 5. Litton J, et al. Presented at: San Antonio Breast Cancer Symposium 2017. December 4-8, 2017; San Antonio, TX. Abs GS6-07. 6. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm623540.htm

7. RUBRACA [prescribing information]. Boulder, CO: Clovis Oncology, Inc., 2016. 8. ZEJULA [prescribing information]. Waltham, MA: TESARO, Inc, 2017.

Courtesy of Kathleen N Moore, MD

GI Toxicities are Common with all PARP Inhibitors (% of pts)

Toxicities	Grade of Tox	Olaparib [1]	Rucaparib[2]	Niraparib[3]
Nausea	All Grades	64	77	73.6
	Grade 3 and 4	3	5	3.0
Constipation	All	20.6[5]	40	39.8
	Grades 3 and 4	0	2	0.5
Vomiting	All	43	46	34.3
	Grades 3 and 4	4	4	1.9
Decreased appetite	All	22	39	25.3
	Grades 3 and 4	1	3	0.3
Abdominal pain	All	43	32	22.6
	Grades 3 and 4	8	3	1.1
Diarrhea	All	31	34	19.1
	Grades 3 and 4	1	2	0.3
Dyspepsia	All	25	10[4]	11.4
	Grades 3 and 4	0	<1%	0
Dysgeusia	All	21[5]	39	10.1
	Grades 3 and 4	0	0.3	0

[1]FDA insert, [2]FDA insert, [3]NOVA NEJM 2016, [4]Swisher Lancet Onc 2016, [5]Ledermann Lancet Oncology 2014

Courtesy of Kathleen N Moore, MD

Hematologic Toxicities

(% of pts)

Toxicities	Grade of Tox	Olaparib[1]	Rucaparib[2]	Niraparib[3]
Decrease in hemoglobin	All Grades	90	67	50.1
	Grades 3 and 4	15	23	25.3
Decrease in platelets	All	30	39	61.3
	Grades 3 and 4	3	6	33.8
Decrease in neutrophil count	All	25	35	30.2
	Grades 3 and 4	7	10	19.6

[1]FDA package insert, [2]FDA package insert, [3]NOVA NEJM 2016

Courtesy of Kathleen N Moore, MD

General Symptoms Common with all PARP Inhibitors

(% of pts)

Toxicities	Grade of Tox	Olaparib [1]	Rucaparib[2]	Niraparib[3]
Fatigue	All Grades	66	77	59.4%
	Grade 3 and 4	8	11	8.2%
Insomnia	All	NR	12%	24.3%
	Grades 3 and 4	NR	0	0.3%
Headaches	All Grades	25[5]	17[4]	25.9
	Grades 3 and 4	0	0[4]	0.3

[1]FDA insert, [2]FDA insert, [3]NOVA NEJM 2016, [4]Swisher Lancet Onc 2016
[5]Ledermann Lancet Oncology 2014

Courtesy of Kathleen N Moore, MD

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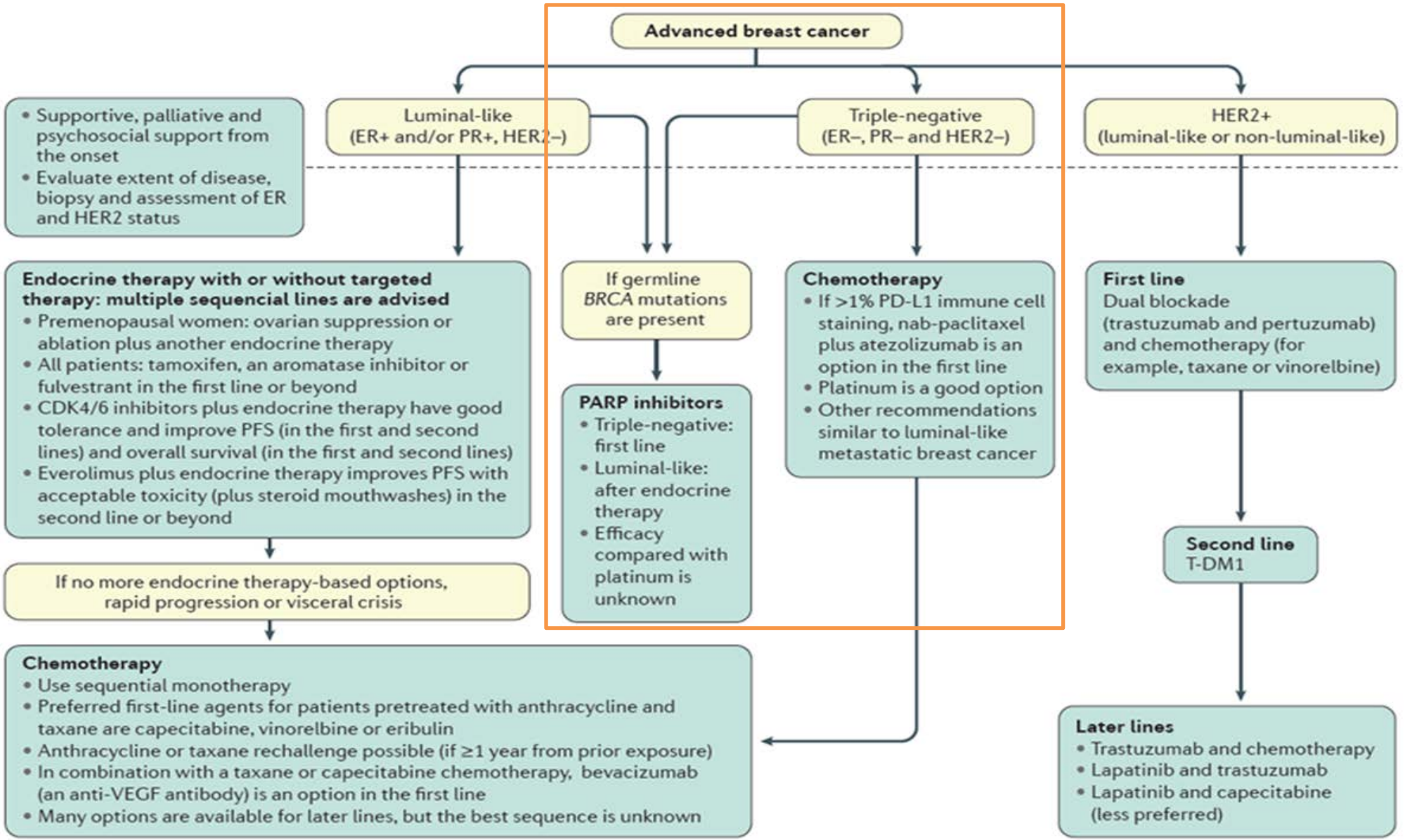
Module 4: PARP Inhibitors for Breast Cancer

- Genomic profile
- Key recent data sets: EMBRACA, OlympiAD, BROCADE
- Current practice patterns
- Ongoing trials

34-year-old woman with ER-positive, HER2-negative breast cancer (from the practice of Ms Fulgencio)

- 2016: Stage 3, ER-positive, PR-negative, HER2-negative left IDC
  - High-risk via Mammaprint, BRCA1 mutation
- Neoadjuvant paclitaxel/pembrolizumab → dd-AC on ISPY2 trial → Bilateral mastectomy/ALND
  - 1.8-cm Grade 3 residual cancer, 7/17 positive nodes, 2 foci of LVI
- Goserelin + letrozole (switched to anastrozole due to joint pain) → RT → Palbocicilb x 1.5 yrs
- 11/2018: Liver and bone metastases
- Continued goserelin + fulvestrant
- T7 compression fracture → Laminectomy, spinal fusion
- Talazoparib + RT to spine
  - Worsening nausea, fatigue; Grade 3 anemia requiring transfusions
- Switched to olaparib, with continued fatigue and anemia → dose reduced to 450 mg/d
- 7 months later: New spinal mets → Olaparib dose increased to 600 mg/d
- Switched back to talazoparib (headaches, malaise, epigastric pain, anemia) x 6 weeks
- NGS: PIK3CA mutation
- Alpelisib x 5 months → PD in liver → capecitabine

Metastatic breast cancer: Treatment strategies

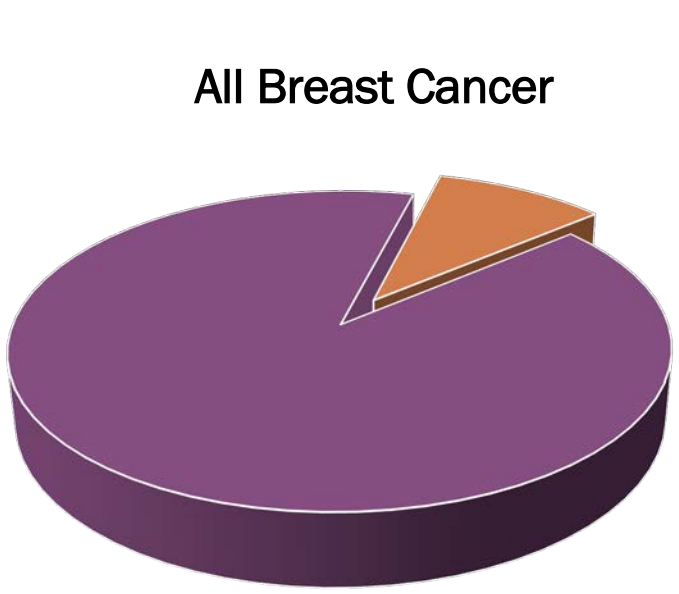


Harbeck et al, 2019

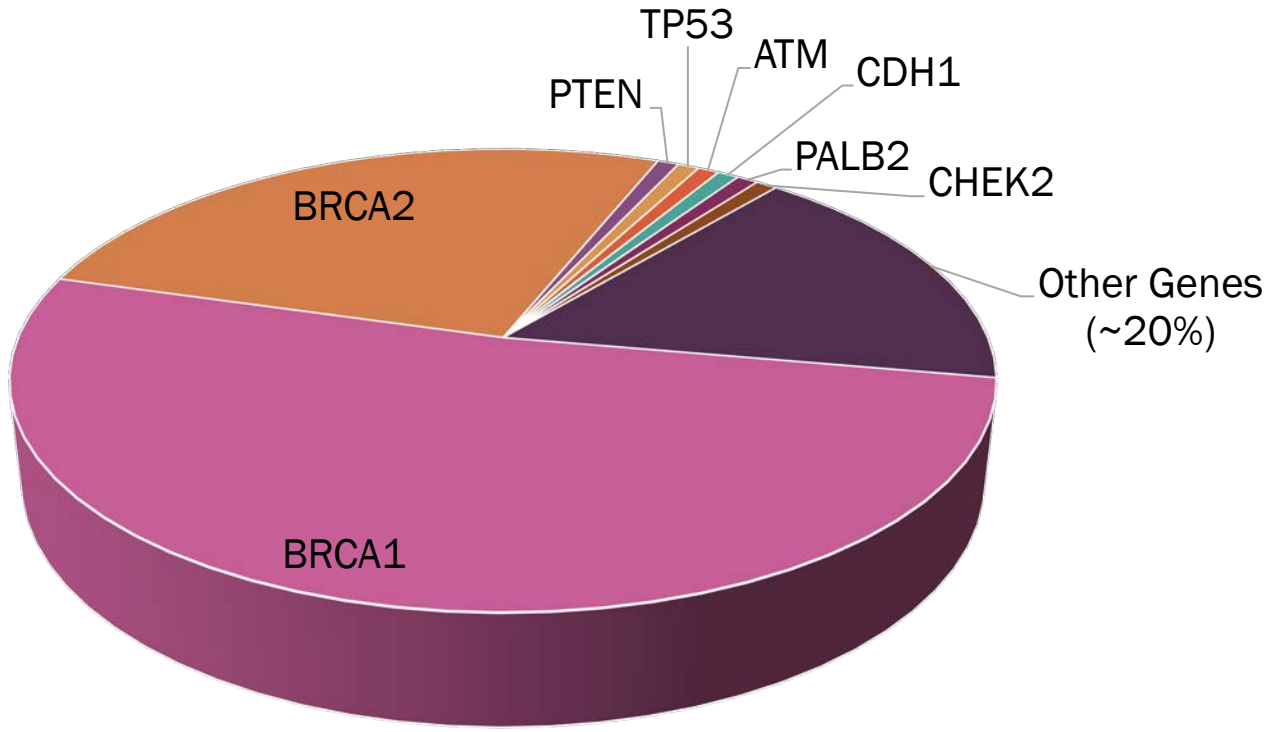
Courtesy of Joyce O'Shaughnessy, MD

Nature Reviews | Disease Primers

Genetic epidemiology of hereditary breast cancer



5-10% Hereditary



Weitzel, 2019 (Personal communciation)

Courtesy of Joyce O'Shaughnessy, MD

A higher proportion of TNBC patients have BRCA mutations than HR+ patients… [1,2]

The majority of TNBC are BRCA1m and HR+ tumours are BRCA2m [1,2]

TNBC patients

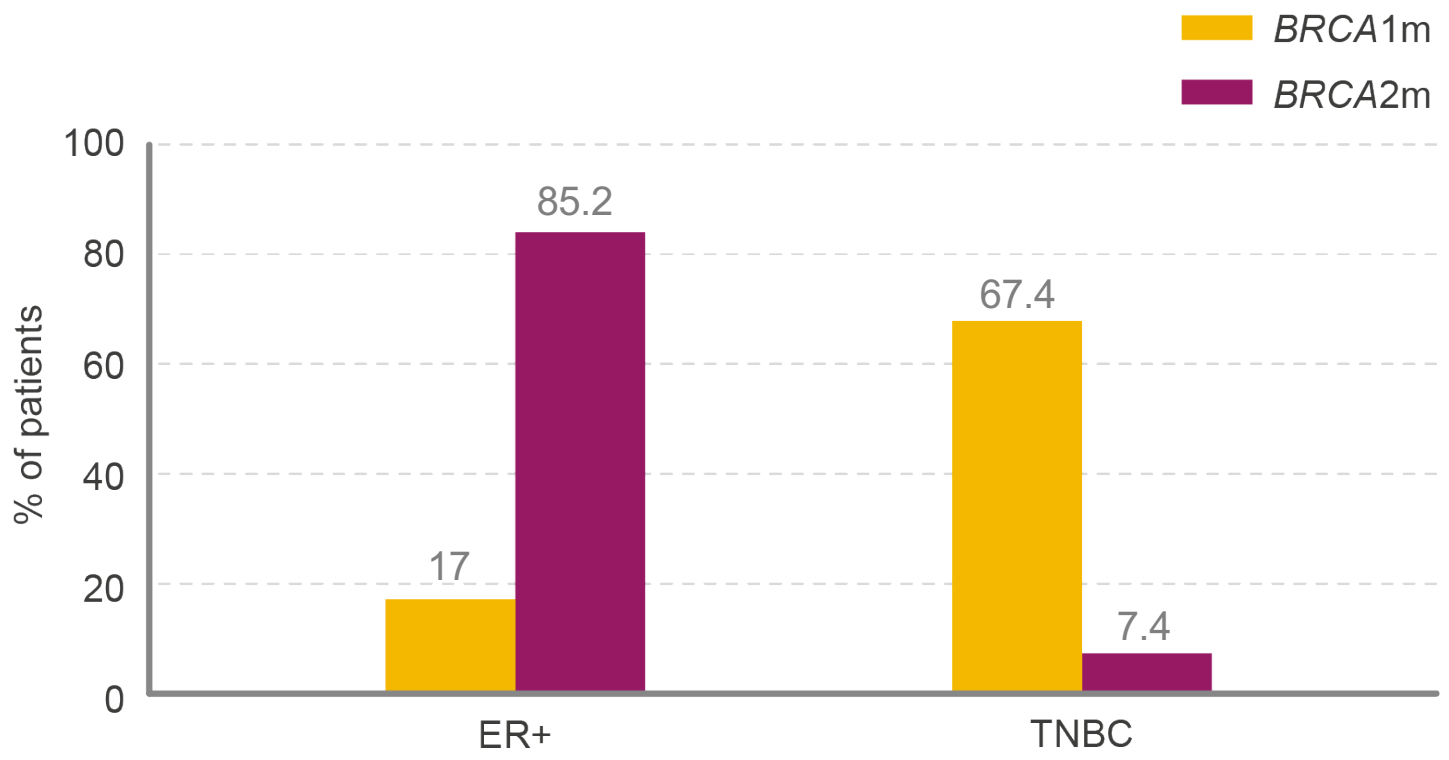
~17%

have *BRCA* mutations

HR+ patients

~6%

have *BRCA* mutations



Note that these calculations are based on very small patient populations.
Detailed analysis of *BRCA*m prevalence, age of onset and survival outcomes are currently lacking for breast cancer subtypes.

*BRCA*m=*BRCA* mutation; TNBC=triple negative breast cancer; HR+=hormone receptor positive; ER+=oestrogen receptor positive

1. Winter et al. Ann Oncol. 2016 Aug; 27(8): 1532–1538; 2. Aleskandarany M, et al. Breast Cancer Res Treat. 2015;150:81-90

Courtesy of Joyce O'Shaughnessy, MD

… But due to the relative prevalence, the majority of BRCA mutations are found in HR+ patients rather than TNBC

Many more breast cancer patients have HR+ disease than TNBC

Estimated prevalence of *BRCA*m within mBC segments

Note that these calculations are based on very small patient populations.
Detailed analysis of *BRCA*m prevalence, age of onset and survival outcomes are currently lacking for breast cancer subtypes.

*BRCA*m=*BRCA* mutation; mBC=metastatic breast cancer; TNBC=triple negative breast cancer; HR+=hormone receptor positive

Winter et al. Ann Oncol. 2016 Aug; 27(8): 1532–1538

Courtesy of Joyce O'Shaughnessy, MD

When and Who to test for *BRCA1/2* mutations?
NCCN Guidelines Recommendations (ABC4 & NCCN)

National Comprehensive Cancer Network: Invasive Breast Cancer[1]

CLINCAL STAGE	WORK-UP
Recurrent or Stage IV (M1)	• History and physical exam • Discuss goals of therapy, adopt shared decision-making, and document course of care • CBC • Comprehensive metabolic panel, including liver function tests and alkaline phosphatase • Chest diagnostic CT with contrast • Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast • Brain MRI with contrast if suspicious CNS symptoms • Spine MRI with contrast if back pain or symptoms of cord compression • Bone scan or sodium fluoride PET/CT (Category 2B) • FDG PET/CT (optional) • X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan • First recurrence of disease should be biopsied • Determination of tumour ER/PR and HER2 status on metastatic site • **For patients with HER2-negative tumours under consideration for chemotherapy, strongly consider germline *BRCA1/2* testing** • Genetic counselling if patient is high-risk for hereditary breast cancer

Courtesy of Joyce O'Shaughnessy, MD

1. National Comprehensive Cancer Network (NCCN). Breast Cancer. Version 1.2019.

Phase III trials of PARP Inhibitors in gBRCA HER2-negative metastatic breast cancer patients

OlympiAD[1]

gBRCAm HER2- mBC

≤2 prior chemotherapy lines for mBC

Previous treatment with anthracycline and taxane in either the (neo)adjuvant or metastatic setting

Randomise 2:1

Olaparib
300mg *po* bid

Treatment of Physician's Choice (TPC)

Primary endpoint
PFS (BICR)

EMBRACA[2]

gBRCAm HER2- LABC or ABC

≤3 prior lines of chemotherapy

Previous treatment with a taxane, an anthracycline, or both, unless this treatment was contraindicated

Randomise 2:1

Talazoparib
1mg *po* qd

Treatment of Physician's Choice (TPC)

Primary endpoint
PFS (BICR)

Courtesy of Joyce O'Shaughnessy, MD

1. Robson et al. N Engl J Med. 2017; 377:523-533;
2. Litton J et al. N Engl J Med 2018; 379:753–763

Agenda

Module 1: Overview of PARP Inhibitors — Biologic Rationale and Mechanism of Action

- Case Presentation: 47-year-old woman with ovarian cancer

Module 2: Side Effects and Toxicities of PARP Inhibitors

Module 3: PARP Inhibitors for Ovarian Cancer

Module 4: PARP Inhibitors for Breast Cancer

- Case Presentation: 34-year-old woman with ER-positive, HER2-negative breast cancer

Module 5: PARP Inhibitors for Pancreatic Cancer

- Case Presentation: 67-year-old man with metastatic pancreatic cancer
- Case Presentation: 68-year-old man with metastatic pancreatic cancer

Module 6: PARP Inhibitors for Prostate Cancer

- Case Presentation: A man in his early 50s with metastatic prostate cancer
- Case Presentation: A 71-year-old man with metastatic prostate cancer

Module 5: PARP Inhibitors for Pancreatic Cancer

- Genomic profile
- Key recent data sets: POLO, RUCAPANC
- Current practice patterns
- Ongoing trials

67-year-old man with metastatic pancreatic cancer (from the practice of Tammy Triglianos, RN, MS, ANP-BC, AOCNP)

- Stage IV BRCA1-mutated pancreatic adenocarcinoma with peritoneal carcinomatosis
- FOLFIRINOX, with response, increasing fatigue → FOLFOX, with progressive neuropathy → maintenance 5-FU → PD
- FOLFIRI, with SD and CA19-9: 161 → 49.5
- Olaparib
  - Dysgeusia, Grade 2 fatigue (olaparib dose reduced to 300 → 250 mg BID)
  - Restaging after 2 months: SD and CA19-9: 49.5 → 39.1
  - After additional 2 months: Progressive GI symptoms → 2-week treatment break, with symptom improvement
  - Re-started olaparib, with recurrent GI symptoms, rising CA19-9 (39.1→96.9→269)
- IV chemotherapy
  - Struggled through last treatment course, passed away

68-year-old man with metastatic pancreatic cancer (from the practice of Ms Triglianos)

- 2013: Stage IV BRCA1-mutated pancreatic adenocarcinoma with liver metastases
- Multiple lines of systemic chemotherapy with one 6-month holiday in 2017
  - CA19-9 never elevated, so not a reliable marker
- 5/2019: Olaparib 200mg BID, dose reduced due to renal insufficiency from focal segmental glomerulosclerosis
  - Initially tolerated treatment fairly well over 5-months
  - Short treatment break due to cervical discectomy from cervical spondylosis
  - After restarting: Fatigue, progressive dysgeusia, decreased appetite with associated weight loss (slight rise in creatinine) → Olaparib held for 1 month (extended due to Christmas holiday)
- Restarted Olaparib at 200 mg BID
- Currently, he continues on therapy with fairly good tolerance, without disease progression

Germline *BRCA1/2* Mutations in Pancreatic Cancer

JOHNS HOPKINS MEDICINE

- 5%-7% of pancreatic cancer patients have a germline *BRCA1* or *BRCA2* mutation
  - Ashkenazi Jewish: 5%-16%
  - Familial PDAC: 5%-19%
  - Familial breast/ovary cancer: 5%-10%

- **40% of patients who are germline *BRCA* gene mutation carriers do NOT have a family history**

Courtesy of Michael Pishvaian, MD, PhD

Hahn SA et al. Gastroenterology. 2003;124:544-560; Murphy KM et al. Cancer Res. 2002;62:3789-3793; Ozçelik H et al. Nat Genet. 1997;16:17-18; Lal G et al. Cancer Res. 2000;60:409-416; Lucas AL et al. Clin Cancer Res. 2013;19:3396-3403; Ferrone C et al. J Clin Oncol. 2009;27:433-438; Stadler ZK et al. Cancer. 2012;118:493-499; Brose MS et al. J Natl Cancer Inst. 2002;94:1365-1372; Holter S et al. J Clin Oncol. 2015;33:3124-3129; Chaffee KG et al. Genet Med. 2018;20:119-127; Petersen GM et al. Semin Oncol. 2016;43:548-553

2019 NCCN Guidelines on Pancreatic Cancer

JOHNS HOPKINS MEDICINE

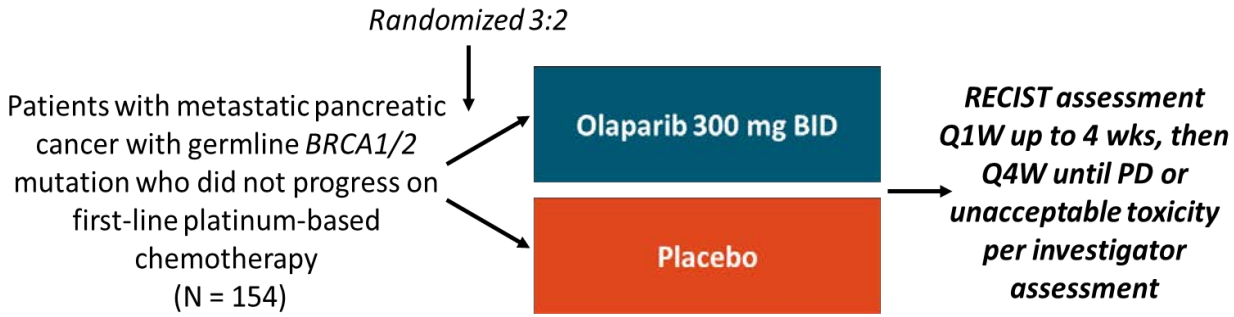
"Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes"

Courtesy of Michael Pishvaian, MD, PhD

NCCN Guidelines. Pancreatic Adenocarcinoma. Version 2.2019; https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf. Accessed April 25, 2019

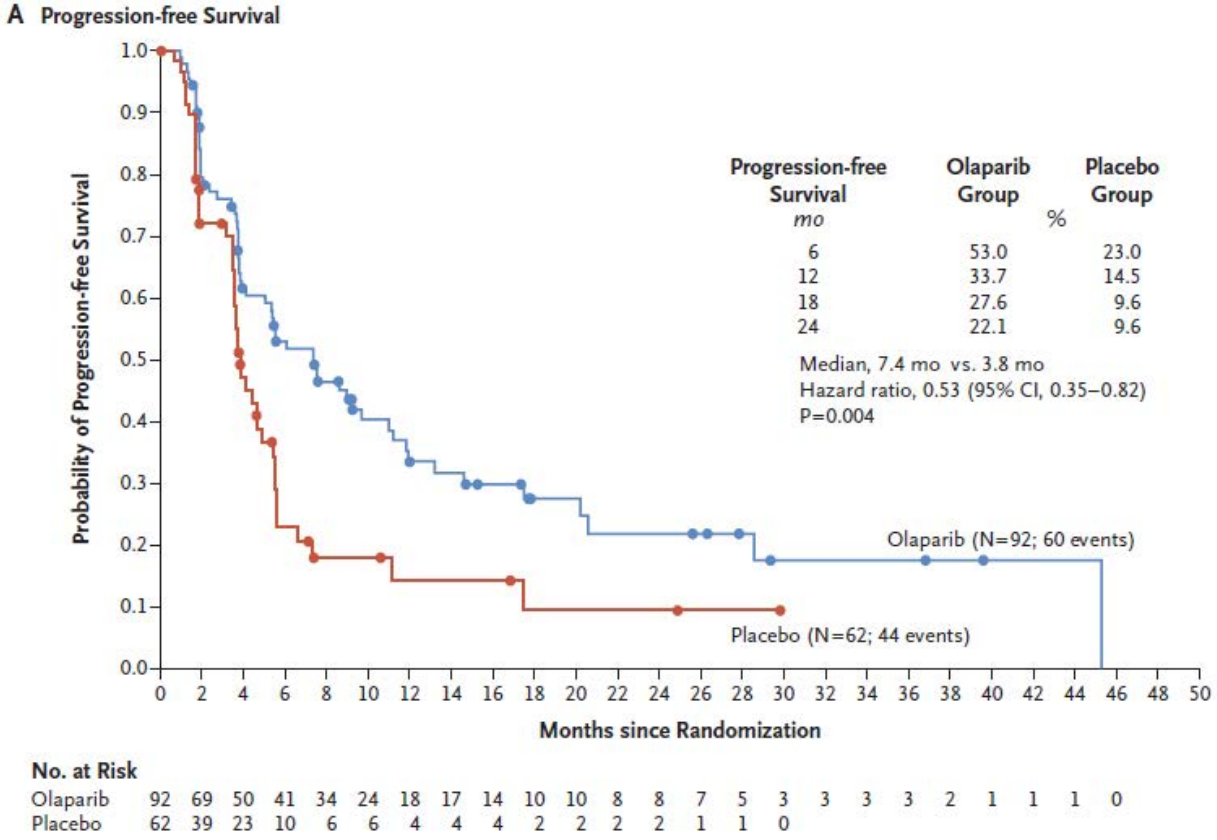
PARP Inhibitors: Phase III Trial

- POLO: Olaparib as Maintenance Therapy in Germline *BRCA1/2*-Mutated Pancreatic Cancer
- Randomized, double-blind phase III trial
  - Improved PFS with olaparib vs. placebo



- 1º endpoint: investigator-assessed PFS (RECIST v1.1)
- 2º endpoints: safety, OS, PFS2, TFST, TSST, TDT, OR, DCR, QoL

Olaparib FDA approved for patients with metastatic pancreatic cancer and a germline BRCA1/2 mutation for use as maintenance therapy after platinum-based therapy



Courtesy of Michael Pishvaian, MD, PhD

Golan T, NEJM, 2019

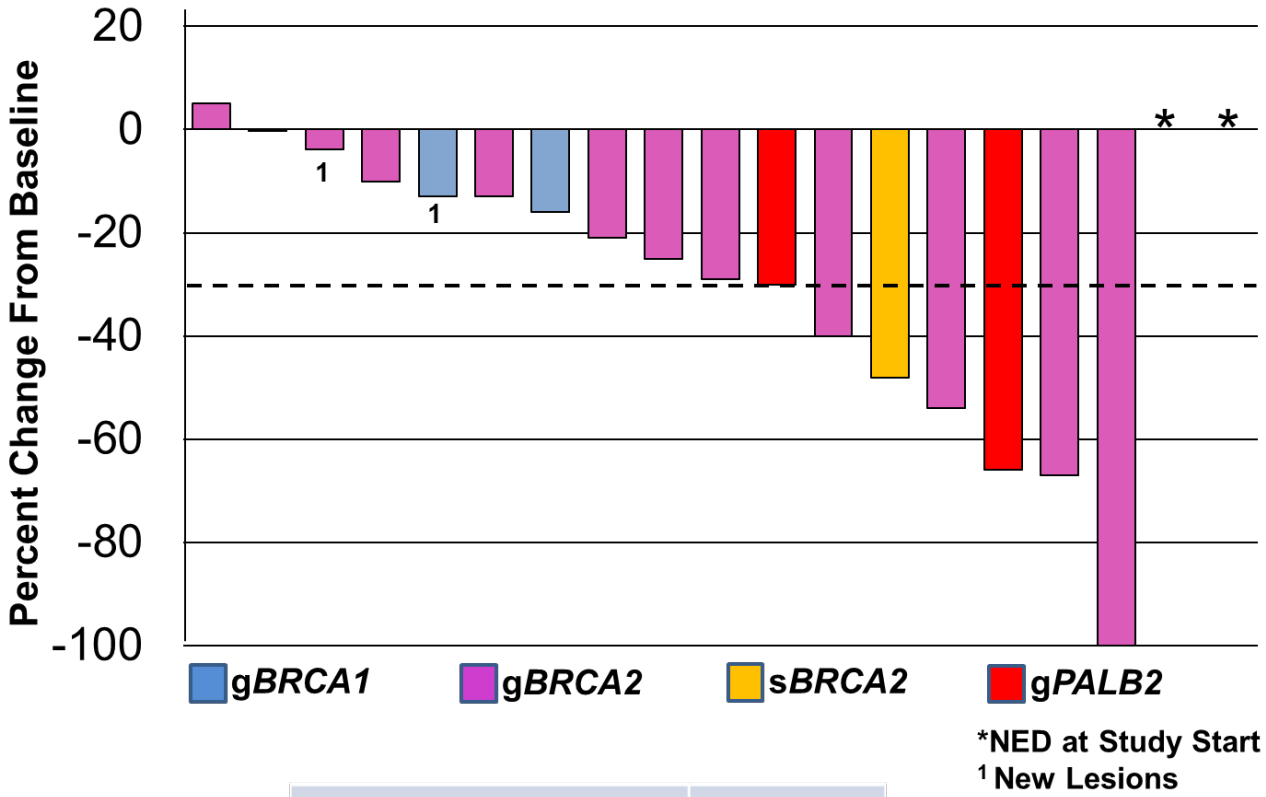
Rucaparib Maintenance for Advanced, Platinum Sensitive *BRCA* or *PALB2* Related Pancreatic Cancer: An Interim Analysis

Kim A. Reiss Binder, Rosemarie Mick, Mark O'Hara, Ursina Teitelbaum, Thomas Karasic, Charles Schneider, Peter J. O'Dwyer, Erica Carpenter, Austin Pantel, Mehran Makvandi, David Mankoff, Katherine Nathanson, Kara Maxwell, Stacy Cowden, Mary Jane Fuhrer, Janae Romeo, Gregory L. Beatty, Susan Domchek.

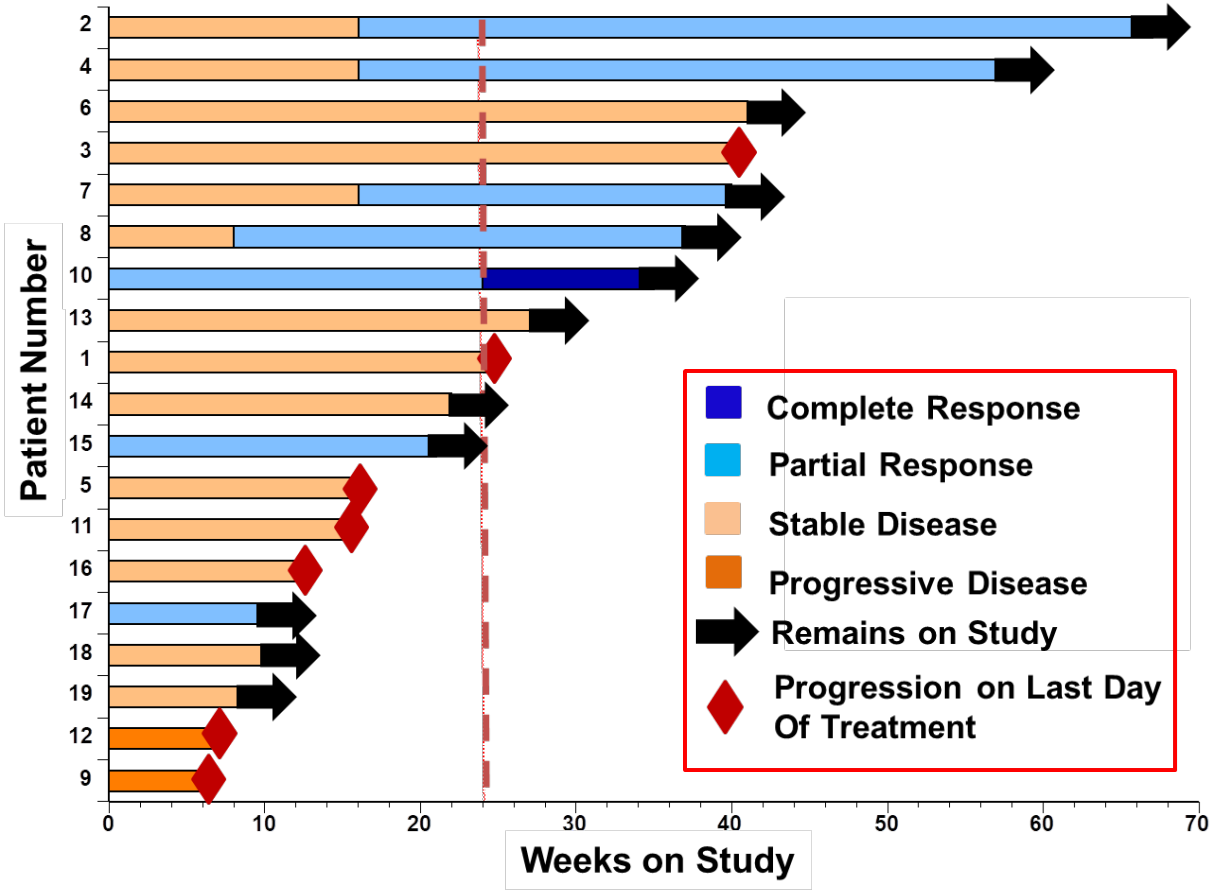
American Association for Cancer Research
2019 Annual Meeting

Courtesy of Michael Pishvaian, MD, PhD

Maintenance Rucaparib



ORR all patients	37.8%
ORR evaluable patients	41.1%
DCR at 8 weeks	89.5%

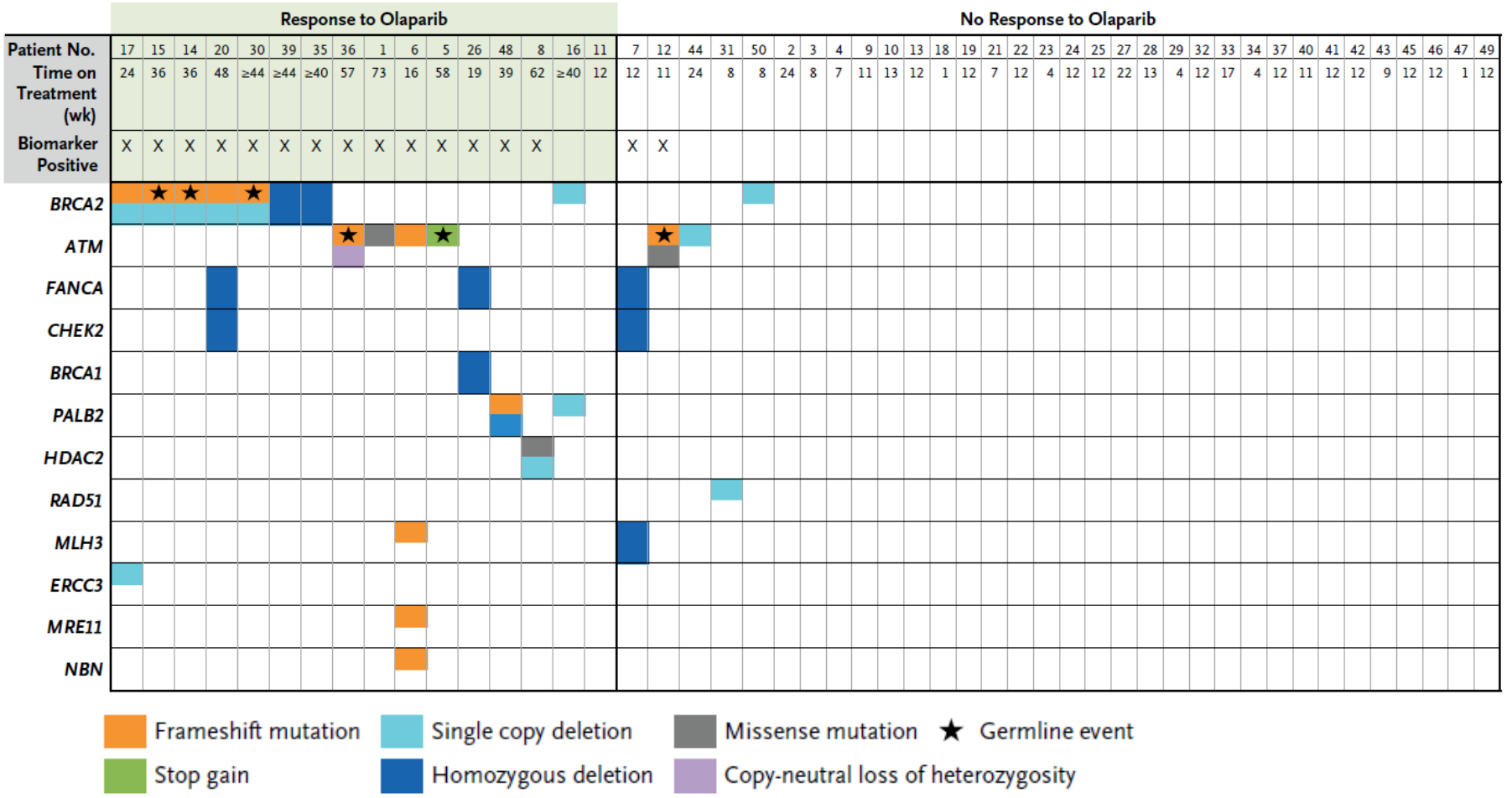


Reiss Binder KA et al. AACR 2019;Abstract CT234.

Courtesy of Michael Pishvaian, MD, PhD

PARP Inhibitors for Other DDR Mutations: Beyond *BRCA1/2*

- Mateo et al – olaparib for prostate cancer
  - 16/49 (33%) responded
  - 16/49 DDR-deficient and 14 responded (88%)
  - Most were NON-*BRCA1/2* mutated



Courtesy of Michael Pishvaian, MD, PhD

Mateo J et al. N Engl J Med. 2015;373:1697-1708

2019 NCCN Guidelines on Pancreatic Cancer

JOHNS HOPKINS MEDICINE

"Tumor/somatic gene profiling is recommended for patients with locally advanced/metastatic disease [80% of patients] who are candidates for anti-cancer therapy to identify uncommon but actionable mutations"

Courtesy of Michael Pishvaian, MD, PhD

NCCN Guidelines. Pancreatic Adenocarcinoma. Version 2.2019; https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf. Accessed April 25, 2019

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Module 6: PARP Inhibitors for Prostate Cancer

- Genomic profile
- Key recent data sets: PROfound, TRITON2, GALAHAD
- Current practice patterns
- Ongoing trials

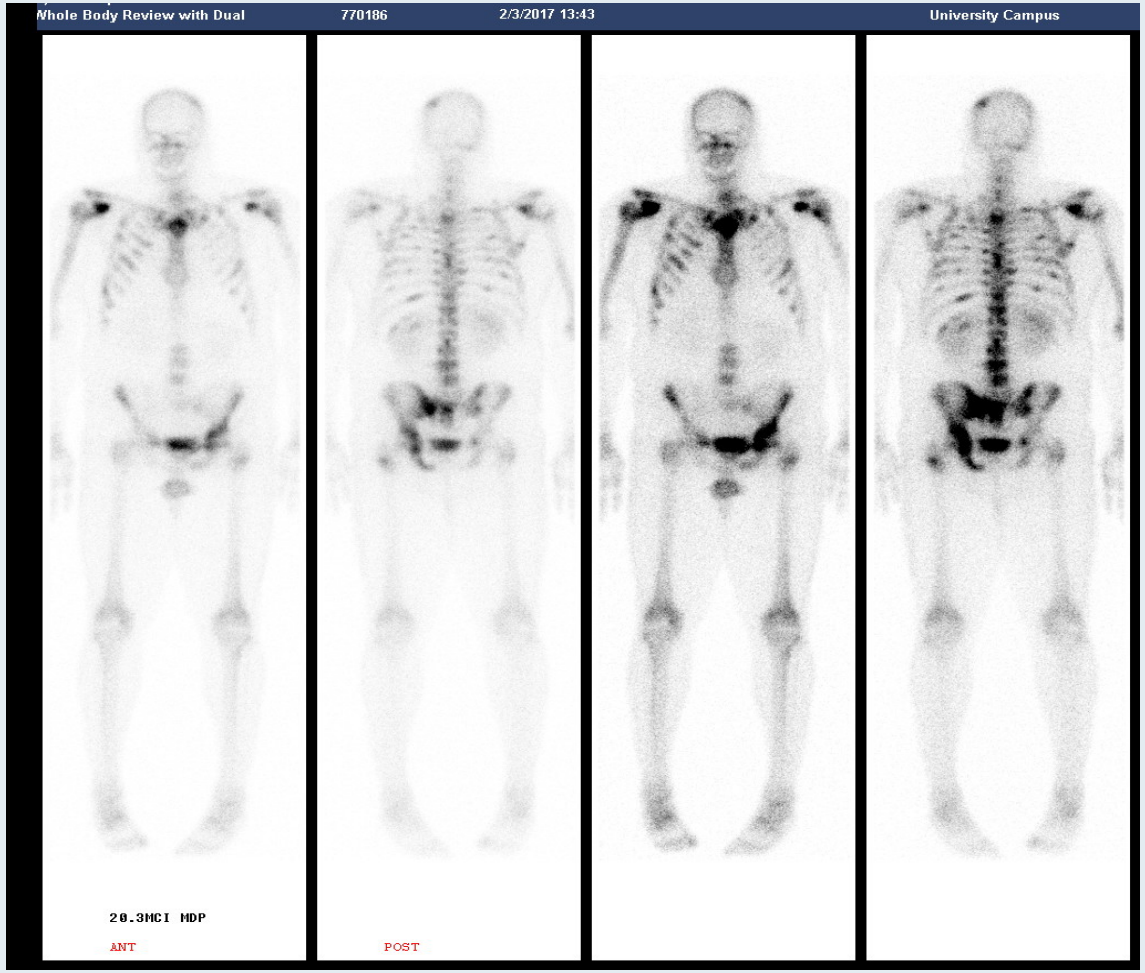
A man in his early 50s with metastatic prostate cancer (from the practice of Erika Meneely, APRN, BC)

- Presents with de novo metastatic prostate cancer (PSA: 591), BRCA2 mutation
- 01/2017 GnRH agonist therapy + bicalutamide + early docetaxel x 6
- 08/2017 Developed castration-resistant disease – GnRH agonist indefinite
- 8/2017 – 6/2018: Enzalutamide (PSA 20→ nadir 0.85)
- 6/2018 – 8/2018: Cabazitaxel (PSA 92 → 313)
- 8/2018 – 10/2018: Abiraterone/prednisone (PSA 391 → 1,110)
- 10/2018: Genetic testing: Somatic BRCA2 mutation
- 10/2018 – 5/2019: Olaparib (PSA 1,110 → nadir 134)
- 5/2019 – 9/2019: Docetaxel (PSA 780 → 17)
- 10/2019 – 12/2019: Carboplatin + docetaxel (PSA 113 → nadir 56)
- 1/2020: Mitoxantrone → discontinued due to PD, transitioned to supportive care/Hospice

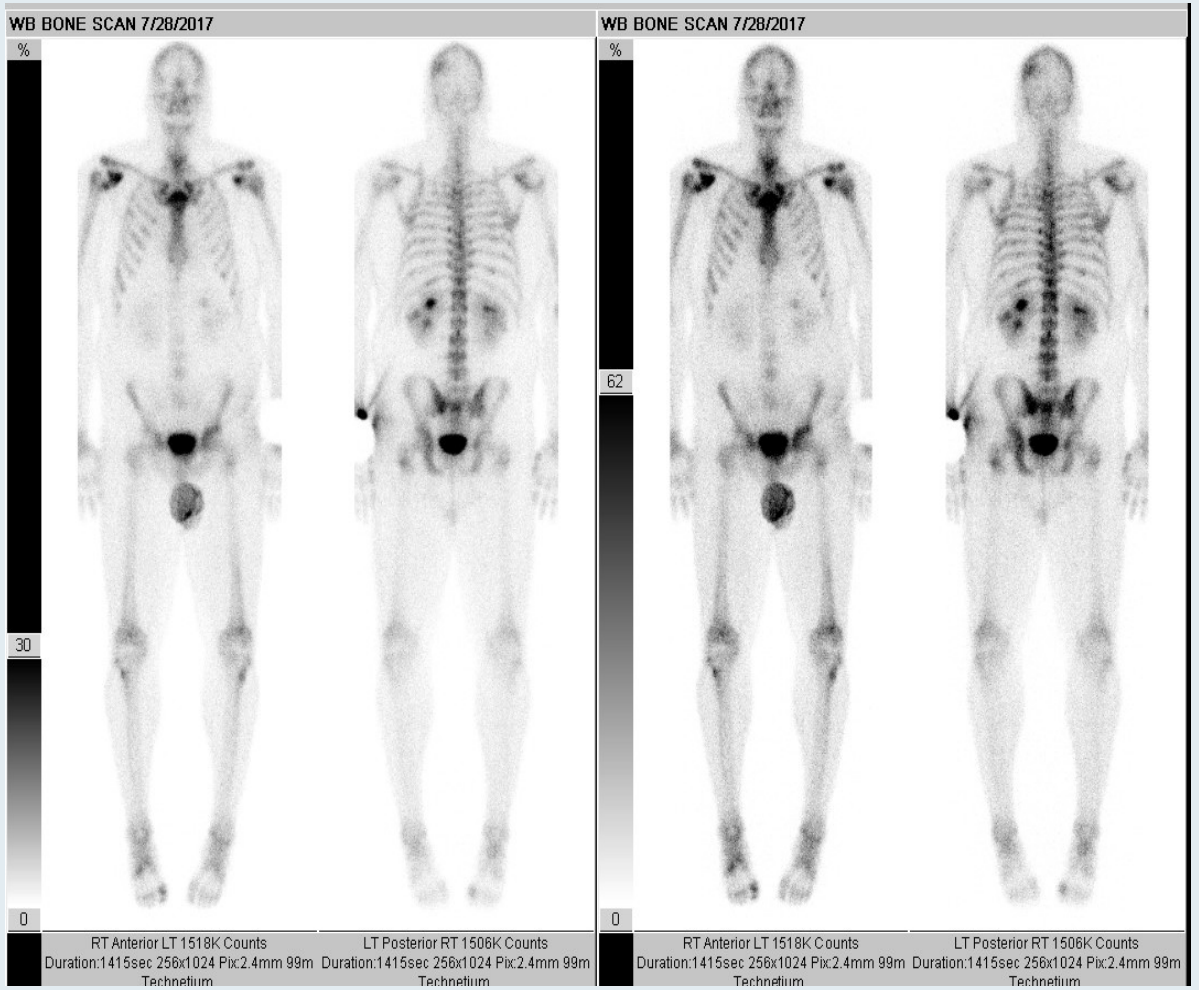
NOTE: PSA progression always associated with intractable nausea/vomiting requiring multiple hospital admissions

A man in his early 50s with metastatic prostate cancer (from the practice of Ms Meneely)

February 2017 (initial bone scan)



July 2017 (post early docetaxel)



A 71-year-old man with metastatic prostate cancer (from the practice of Ms Meneely)

- Intermediate risk (3+4=7) localized prostate cancer (PSA <10), BRCA2 carrier
- 2004: Definitive EBRT with ADT x 7 months
- 10/2015: Biopsy-proven bone metastases
  - Initiated life-long ADT (Pretreatment PSA: 6)
- 2/2017: Developed castration-resistant disease
- 3/2016 – 3/2017: Olaparib (PSA 13 → nadir 5)
  - Cough, fatigue and anorexia → dose reduction

DNA Repair Mutations in Advanced Prostate Ca

	SOMATIC	GERMLINE
BRCA2	8-9%	5%
BRCA1	1-2%	1%
ATM	5-6%	2%
All Other	6-7%	2-3%
TOTAL	**20-25%**	**10-12%**

Robinson D, et al. CELL. 2015; 5: 1215-1228.
Pritchard CC, et al. NEJM. 2016;375:443-453.

Courtesy of Emmanuel S. Antonarakis, MD

NCCN PCa Guidelines (v1.2020, 3/16/2020): *Germline*

National Comprehensive Cancer Network®

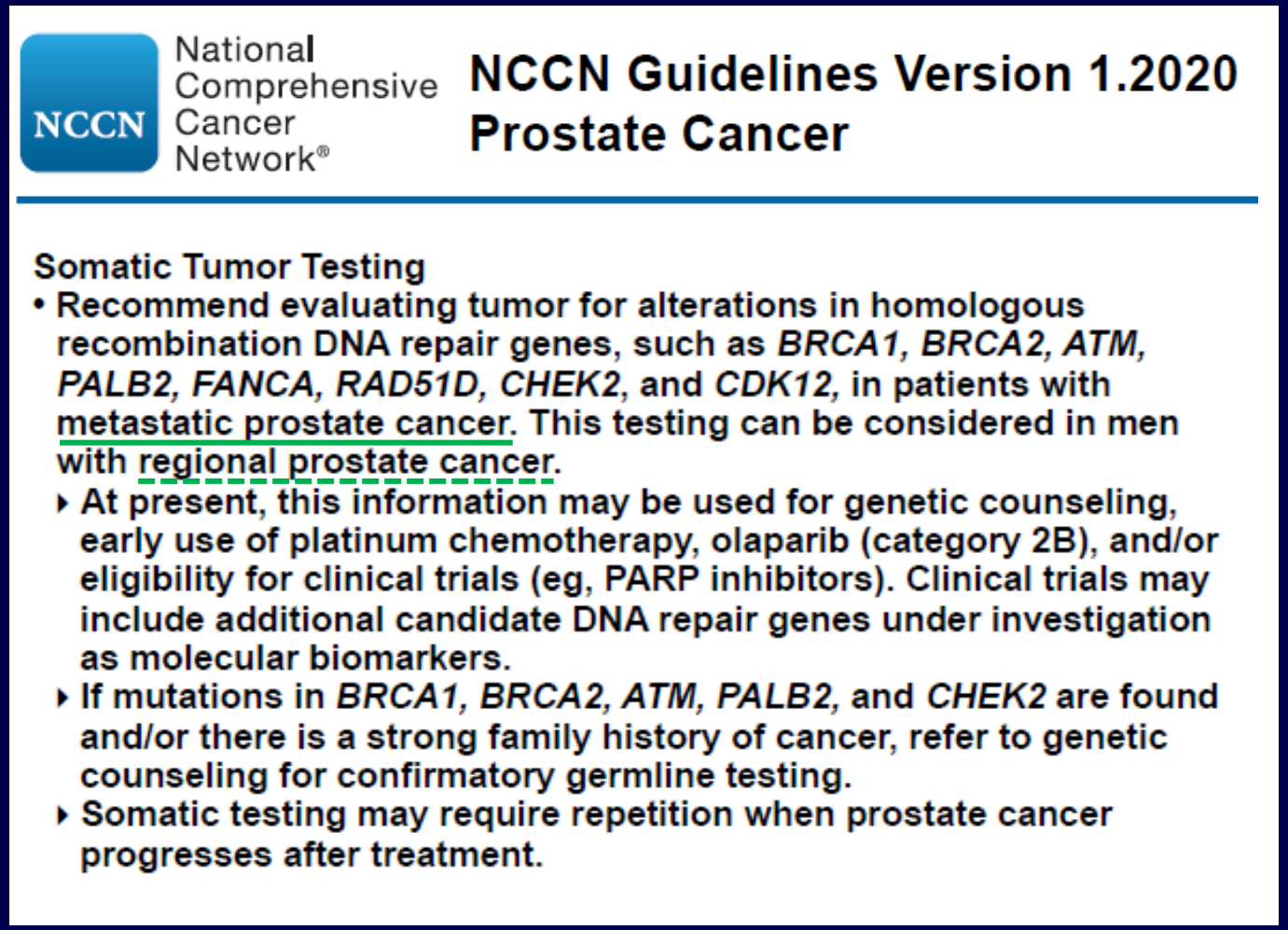
NCCN Guidelines Version 1.2020
Prostate Cancer

- Germline genetic testing is recommended for patients with prostate cancer and any of the following:
  - High-risk, very-high-risk, regional, or metastatic prostate cancer
  - Ashkenazi Jewish ancestry
  - Family history of high-risk germline mutations (eg, *BRCA1/2*, Lynch mutation)
  - A positive family history of cancer:
    - A strong family history of prostate cancer consists of: brother or father or multiple family members who were diagnosed with prostate cancer (but not clinically localized Grade Group 1) at <60 years of age or who died from prostate cancer
      OR
    - ≥3 cancers on same side of family, especially diagnoses ≤50 years of age: bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (but not clinically localized Grade Group 1), small bowel, or urothelial

NCCN Prostate Cancer Guidelines, Version 1.2020 — March 16, 2020.

Courtesy of Emmanuel S. Antonarakis, MD

NCCN PCa Guidelines (v1.2020, 3/16/2020): *Somatic*



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NCCN Guidelines Version 1.2020
Prostate Cancer

Somatic Tumor Testing

- Recommend evaluating tumor for alterations in homologous recombination DNA repair genes, such as *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*, and *CDK12*, in patients with metastatic prostate cancer. This testing can be considered in men with regional prostate cancer.
  - At present, this information may be used for genetic counseling, early use of platinum chemotherapy, olaparib (category 2B), and/or eligibility for clinical trials (eg, PARP inhibitors). Clinical trials may include additional candidate DNA repair genes under investigation as molecular biomarkers.
  - If mutations in *BRCA1, BRCA2, ATM, PALB2,* and *CHEK2* are found and/or there is a strong family history of cancer, refer to genetic counseling for confirmatory germline testing.
  - Somatic testing may require repetition when prostate cancer progresses after treatment.

NCCN Prostate Cancer Guidelines, Version 1.2020 — March 16, 2020.

Courtesy of Emmanuel S. Antonarakis, MD

Testing Platforms (panel-based NGS preferred)

- Germline genetic testing
  - Blood (leukocytes), or saliva
- Somatic genomic testing
  - Tissue/biopsy-based
  - Blood-based/ctDNA

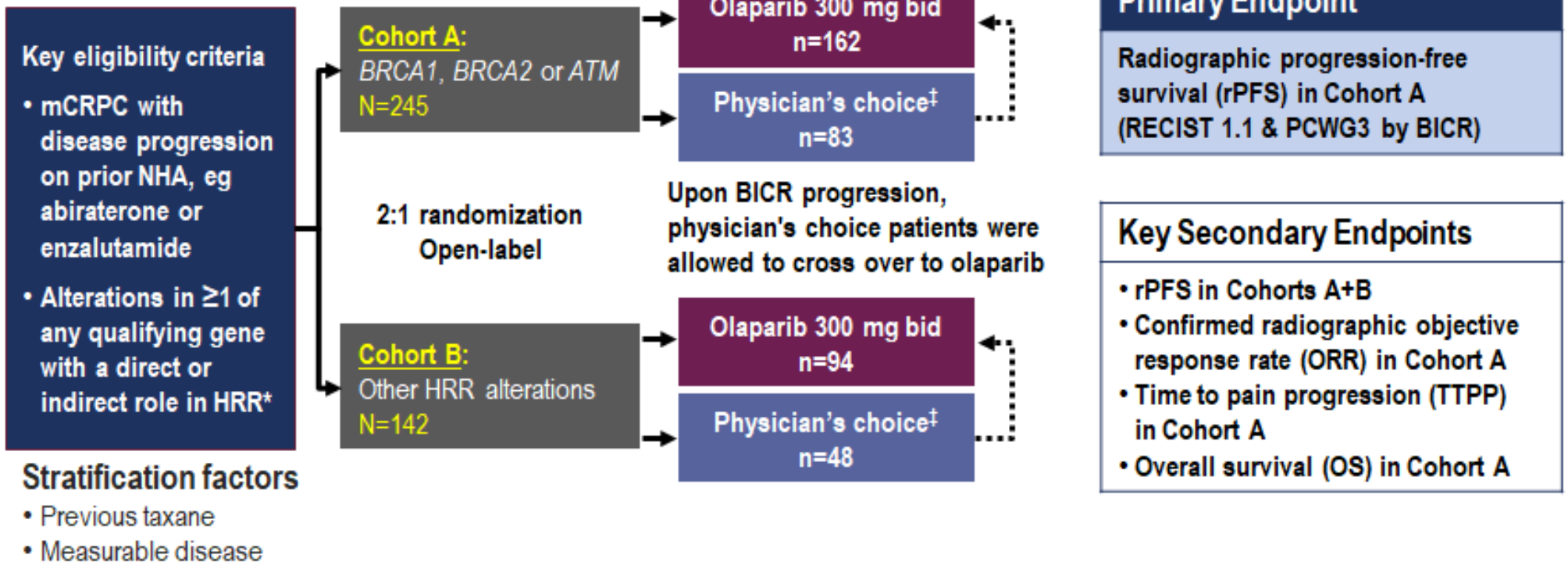
Courtesy of Emmanuel S. Antonarakis, MD

Olaparib in mCRPC

19 May 2020 – Olaparib was FDA approved for mCRPC patients with a HRR gene mutation, who have previously received abiraterone or enzalutamide

Courtesy of Emmanuel S. Antonarakis, MD

PROfound (phase 3 study): Olaparib vs Enza or Abi in mCRPC with somatic HRD mutations



*An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test

Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

ClinicalTrials.gov. NCT02987543

Courtesy of Emmanuel S. Antonarakis, MD

PROfound: Summary by Cohort

	Cohort A	Cohort B	Cohorts A+B
N (Olaparib/ Physician's choice)	162/ 83	94/ 48	256/ 131
rPFS (BICR)			
Hazard ratio (95% CI)	0.34 (0.25, 0.47) P<0.0001	0.88 (0.58, 1.36)	0.49 (0.38, 0.63) P<0.0001
ORR (BICR)			
%, Olaparib vs Physician's Choice Odds ratio (95% CI)	33.3 vs 2.3% 20.86 (4.18, 379.18) P<0.0001	3.7 vs 8.3% Not calculated†	21.7 vs 4.5% 5.93 (2.01, 25.40)
OS (interim)			
Hazard ratio (95% CI)	0.64 (0.43, 0.97) P=0.0173	0.73 (0.45, 1.23)	0.67 (0.49, 0.93)

Cohort A = Patients with at least 1 alteration in *BRCA1*, *BRCA2* or *ATM*

Cohort B = Patients with alterations in any of 12 other prespecified genes

Hussain M, et al. ESMO 2019; *Ann Oncol* 30(suppl 5): v851-v934. De Bono J, et al. NEJM 2020; epub ahead of print

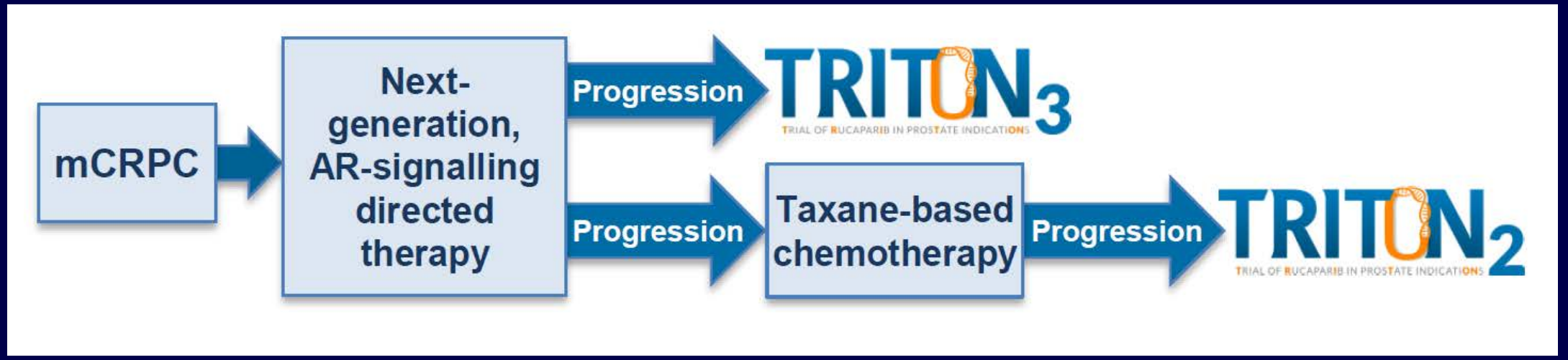
Courtesy of Emmanuel S. Antonarakis, MD

Rucaparib in mCRPC

15 May 2020 – Rucaparib was FDA approved for mCRPC patients with a *BRCA1/2* mutation, who have previously received both a novel hormonal agent and a taxane-based chemotherapy

Courtesy of Emmanuel S. Antonarakis, MD

Rucaparib (TRITON2 and TRITON3)



HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*)

Chowdhury S, et al. ESMO 2018; abstract 795PD.

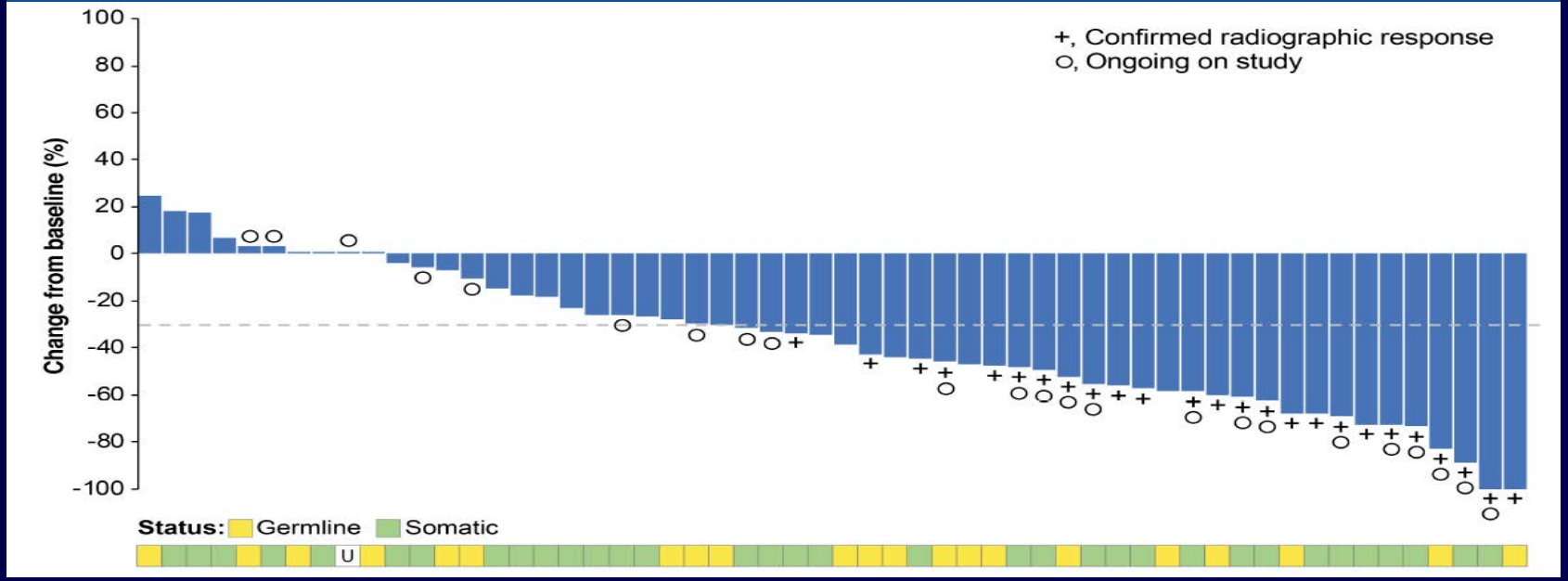
Courtesy of Emmanuel S. Antonarakis, MD

Rucaparib: TRITON2, objective responses

Table 2. Confirmed Investigator-Assessed ORR in Rucaparib-Treated Patients

	DDR gene				
	BRCA1/2 **(n=57)**	***ATM*** **(n=21)**	***CDK12*** **(n=9)**	***CHEK2*** **(n=5)**	**Other (n=13)**
ORR, n (%) [95% CI][a]	25 (43.9) [30.7–57.6]	2 (9.5) [1.2–30.4]	0 [0.0–33.6]	0 [0.0–52.2]	5 (38.5) [13.9–68.4]
Complete response, n (%)	3 (5.3)	0	0	0	1 (7.7)[b]
Partial response, n (%)	22 (38.6)	2 (9.5)	0	0	4 (30.8)[c]
Stable disease, n (%)	26 (45.6)	10 (47.6)	5 (55.6)	3 (60.0)	6 (46.2)
Progressive disease, n (%)	5 (8.8)	8 (38.1)	3 (33.3)	2 (40.0)	1 (7.7)
Not evaluable, n (%)	1 (1.8)	1 (4.8)	1 (11.1)	0	1 (7.7)

Figure 2. Best Change from Baseline in Sum of Target Lesions in Rucaparib-Treated Patients with *BRCA1/2* Alteration (n=56)



Courtesy of Emmanuel S. Antonarakis, MD

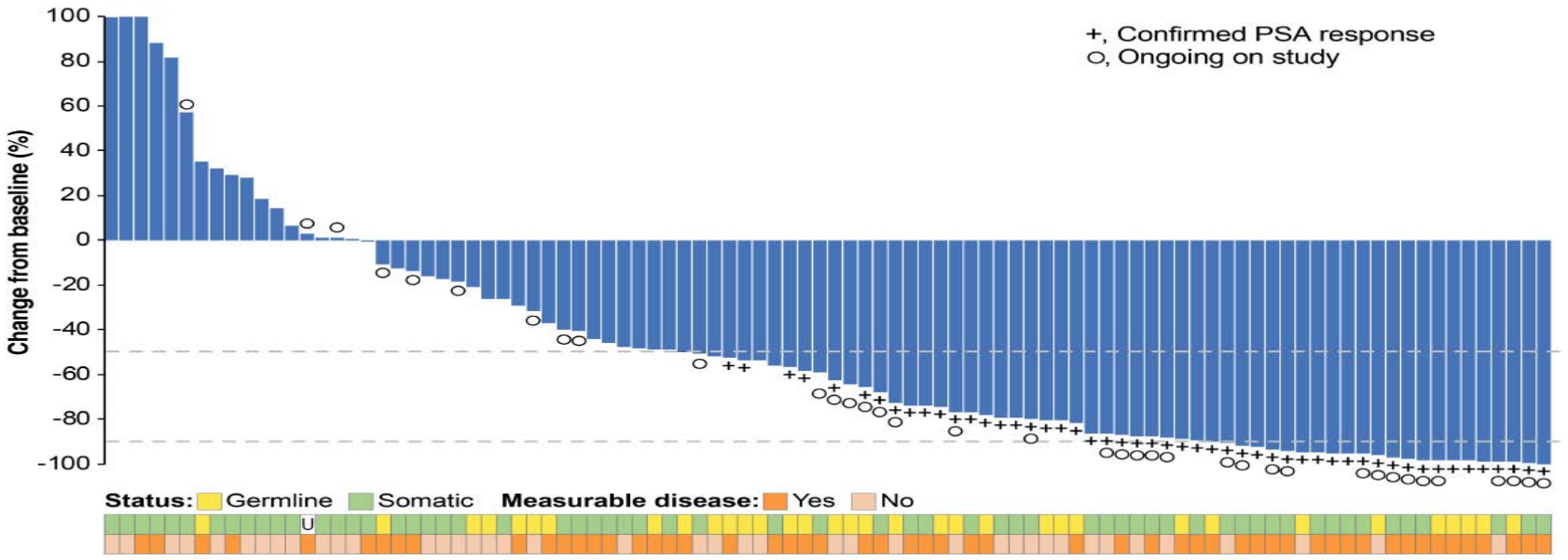
Abida W, et al. ESMO 2019; *Ann Oncol* 30(suppl 5):v325-v355.

Rucaparib: TRITON2, PSA responses

Table 3. Confirmed PSA Response Rates (≥50% Decrease) in Rucaparib-Treated Patients

	DDR gene				
	BRCA1/2	*ATM*	*CDK12*	CHEK2	Other
PSA response rate, n/N (%) [95% CI]					
All evaluable patients	51/98 (52.0) [41.7–62.2]	2/57 (3.5) [0.4–12.1]	1/14 (7.1) [0.2–33.9]	1/7 (14.3) [0.4–57.9]	5/14 (35.7) [12.8–64.9][a]
With measurable disease	34/57 (59.6) [45.8–72.4]	2/21 (9.5) [1.2–30.4]	1/9 (11.1) [0.3–48.2]	1/5 (20.0) [0.5–71.6]	5/13 (38.5) [13.9–68.4]
With no measurable disease	17/41 (41.5) [26.3–57.9]	0/36 (0) [0.0–9.7]	0/5 (0) [0.0–52.2]	0/2 (0) [0.0–84.2]	0/1 (0) [0–97.5]
Median time to PSA progression, mo [95% CI]	6.5 [5.7–7.5]	3.1 [2.8–3.7]	3.5 [2.8–4.6]	5.6 [2.8–NR]	5.8 [2.8–NR]

Figure 4. Best Change from Baseline in PSA in Rucaparib-Treated Patients with a *BRCA1/2* Alteration (n=96)



Courtesy of Emmanuel S. Antonarakis, MD

Abida W, et al. ESMO 2019; *Ann Oncol* 30(suppl 5):v325-v355.

Thank you for joining us!

CNE (NCPD) credit information will be emailed to each participant tomorrow morning.